

1 AP12 Rec'd PCT/PTO 18 JAN 2006

HIGH STRENGTH BIORESORBABLE CO-POLYMERS

The present invention relates to polymer compositions and artefacts made therefrom. In particular the present invention relates to
5 polymers having high mechanical strength and their use for the manufacture of load bearing medical devices suitable for implantation within the body. More particularly the invention relates to bioresorbable glycolic acid-containing co-polymers and to implantable medical devices made therefrom.

10 Polymer compositions comprising poly-glycolic acid (PGA) and glycolic acid-containing co-polymers have an established use for medical implants. It has also been proposed that certain mechanical properties may be improved by extruding PGA melts or by drawing PGA in a plastic state. Isotropic PGA has a tensile strength of
15 between 50 to 100 MPa and a tensile modulus of between 2 and 4 GPa. A commercial product (SR-PGA) comprising PGA fibres in a PGA matrix has a flex strength and modulus of 200 – 250 MPa and 12 – 15 GPa, respectively. It is also reported in the literature that melt spun PGAs have tensile strength of about 750 MPa and a
20 modulus from 15 to 20 GPa. In US Patent No. 4968317 an example of a drawn PGA is stated to have a tensile strength of about 600MPa.

Although PGAs having improved strength characteristics are known, none of the known materials have the mechanical properties
25 approaching those of the metals conventionally used for load bearing implantable medical devices. A commercial alloy used for orthopaedic implant devices, known as Ti-6-4, comprises titanium with 6% aluminium and 4% vanadium and has a tensile strength in the range of 800 to 1000MPa and a modulus in the order of 100GPa,

One possible reason that PGA and glycolic acid-containing co-polymers cannot currently be processed to achieve the desired strength of metals is that when the polymers are processed by common methods to produce orientated fibres (e.g. stretching the material at a constant rate in a heated chamber or tank) additional polymer crystallisation occurs during the process. The crystals in the polymer act such that they prevent further polymer orientation. This crystallisation of the polymer limits the mechanical properties that can be achieved by drawing glycolic acid-containing co-polymers to around 800MPa, as described in the prior art.

We have found that polymer compositions comprising glycolic acid-based co-polymers may be processed such that the resultant composition has significantly greater strength, typically of the order of greater than 1100MPa or 1150MPa or 1200MPa with a commensurate increase in modulus, typically in excess of 20GPa, 21 GPa or 22 GPa.

In accordance with the present invention there is provided a polymer composition comprising glycolic acid as a co-polymer with at least one other bioresorbable monomer, or a functional derivative of said co-polymer, having a tensile strength of at least 1200MPa.

In accordance with the present invention there is provided a polymer composition comprising glycolic acid as a co-polymer with at least one other bioresorbable monomer, or a functional derivative of said co-polymer, having a tensile strength of at least 1100MPa.

The polymer composition gains this level of tensile strength by means of a novel processing method that results in an orientated structure, for example an orientated fibre.

The present invention further provides an artefact comprising a polymer composition including glycolic acid or a functional derivative thereof having a tensile strength of at least 1200MPa.

The present invention also provides an artefact comprising a polymer composition including glycolic acid or a functional derivative thereof having a tensile strength of at least 1100MPa.

5 The polymer composition may be comprised entirely of glycolic acid-based co-polymer or a derivative thereof, or may comprise a glycolic acid-based co-polymer-containing blend with other polymers. Preferably the polymer composition is entirely glycolic acid-based co-polymer.

10 Similarly, artefacts formed from the polymer compositions of the invention may consist wholly of the polymer compositions of the invention or may be composites consisting only partially of the polymer compositions of the invention.

15 Aptly the artefact contains 10 to 80% by volume of the polymer compositions of the invention, suitably the artefact contains up to 60% by volume of the polymer compositions of the invention, preferably the artefact contains at least 40% by volume of the polymer compositions of the invention and typically the artefact contains approximately 50% by volume of the polymer compositions of the invention.

20 We have found that in order to achieve the high strength exhibited by the compositions of the invention it is necessary that the glycolic acid-containing co-polymer be rendered into an amorphous state and then immediately drawn to form a highly orientated structure.

25 This can be achieved by first processing isotropic glycolic acid-based co-polymer granules to form fibres or filaments, thereafter passing the fibres into a quenching bath to form an amorphous structure. Polymer compositions of the present invention may then be produced by drawing the quenched, amorphous glycolic acid based co-polymer. Preferably this is a drawing process which

minimises the time polymer is exposed to elevated temperatures, thus minimising the time for the polymer to crystallise.

In accordance with another aspect of the invention there is provided
5 a process for the manufacture of glycolic acid-based co-polymer compositions comprising increasing polymer chain orientation of a substantially amorphous polymer by drawing at localized points within the mass.

Suitably this comprises the steps of forming glycolic acid-based co-
10 polymer or a functional derivative thereof into fibres, for example by melt extrusion or solution spinning; quenching the fibres then subjecting the quenched fibres to a tension under conditions whereby a defined region of the tensioned fibres is drawn.

Aptly fibres of amorphous glycolic acid-based co-polymer-containing
15 polymers may be prepared by solution spinning or melt extruding the polymer through a die; the filament is then rapidly chilled to produce a substantially amorphous material. Typical chilling methods include blowing a cold gas onto the filament as it is produced or by passing the filament through a bath of a suitable cold liquid, e.g. water,
20 silicone oil.

A suitable drawing method is zone heating. In this process a localised heater is moved along a length of fibre which is held under constant tension. This process is used in the zone-drawing process as described by Fakirov in Oriented Polymer Materials, S Fakirov,
25 published by Hüthig & Wepf Verlag, Hüthig GmbH. In order to carry out this zone heating fibre can be passed through a brass cylinder. A small part of the cylinder inner wall is closer to the fibre, this small region locally heats the fibre, compared to the rest of the brass cylinder, localising the drawing of the fibre to this location, see figure
30 1. A band heater can be placed around the brass cylinder to allow it

- to be heated above room temperature. This heated brass cylinder can then be attached to the moving cross-head of a tensile testing machine and the fibre to be drawn suspended from a beam attached to the top of the testing machine. To draw the fibre a weight
- 5 can be attached to the lower end of the fibre, the brass cylinder heated to the desired temperature and the cross-head moved to the lower end of the fibre, see figure 2. The polymer draws where the fibre is closest to the brass cylinder, as the cross-head is moved up the length of the fibre, then a length of the fibre can be drawn.
- 10 Suitably the fibre can be held taut using a small stress, which is typically below the yield point of the material at ambient temperatures. The fibre can then be heated locally to a temperature which is above the softening point (T_g) but below the melting point such that localised drawing of the polymer occurs, the whole fibre
- 15 can be treated by movement of either or both the fibre and heated zone such that the full length of the fibre is drawn. This first drawing of the polymer may produce a polymer with improved molecular alignment and therefore strength and modulus. In this first step the conditions are selected such that the material does not substantially
- 20 crystallise during the process, this requires that either the temperature of the polymer is below the temperature at which crystallisation occurs, T_c , or if the polymer is above T_c the speed at which the heated zone moves along the fibres is fast enough such that the polymer cools below T_c before it has time to crystallise.
- 25 Further improvements can be made by subsequent treatments, where the stress applied to the fibre or the zone temperature is increased or both. Both the strength of the fibre and the softening point increase as the degree of molecular alignment improves. The process can be repeated many times, until the desired properties are
- 30 reached. A final annealing step can be carried out in which the material crystallises under tension in the process; this can further improve the mechanical properties and improve the thermal stability of the final fibre.

In an embodiment of this aspect of the invention there is provided an artefact comprising a poly-glycolic acid in accordance with the invention. For example, the glycolic acid-containing co-polymer fibres can be mixed with other components to form the artefacts.

- 5 These other components may be polymers, bioresorbable polymers, non-polymeric materials or combinations thereof.

Aptly the bioresorbable polymer comprises a poly-hydroxy acid, a poly-caprolactone, a polyacetal, a poly-anhydride or mixture thereof; the polymer comprises poly-propylene, poly-ethylene, poly-methyl
10 methacrylate, epoxy resin or mixtures thereof whilst the non-polymeric component comprises a ceramic, hydroxyapatite, tricalcium phosphate, a bioactive factor or combinations thereof.

Suitably the bioactive factor comprises a natural or engineered protein, a ribonucleic acid, a deoxyribonucleic acid, a growth factor,
15 a cytokine, an angiogenic factor or an antibody.

Artefacts according to the present invention can aptly be manufactured by placing appropriate lengths of strengthened glycolic acid-containing co-polymer fibre into moulds, adding the other components then compression moulding. Alternatively, the
20 strengthened fibres can be pre-mixed with the other components then compression moulded.

In an alternative processing method, artefacts according to the present invention can be manufactured by forming a polymeric component in the presence of the strengthened fibres by in situ
25 curing of monomers or other precursors for said polymeric component.

Preferably the monomers used in this process do not liberate any by-products on polymerisation as these can compromise the properties of the artefact.

Aptly at least one of the monomers used in said in situ curing process is a ring-opening monomer that opens to form a polyhydroxy acid. Typically at least one monomer is a lactide, a glycolide, a caprolactone, a carbonate or a mixture thereof.

- 5 The polymer itself may be produced from reacting/incorporating/combining or by other means the glycolide or glycolic acid with at least one other monomer.

Incorporation of the at least one other monomer into the polymer composition can be achieved by any known means and for example
10 maybe by ring polymerisation or transesterification.

Suitable monomers may include ring opening monomers like for instance lactide (& its isomers), trimethylene, carbonate, p-dioxanone, ϵ -caprolactone, 2-methyl glycolide, 2,3,2-dimethyl glycolide, 1,5-dioxapane, 1,4-dioxapane, 3,3-dimethyltrimethylene
15 carbonate, glycosalicate, depsipeptides (morpholine 2,5-dione and related structures).

Aptly other suitable monomers may include Hydroxyacids, for instance including, lactic acid, caproic acid, hydroxyl benzoic acid and aminoacid esters.

- 20 In other embodiments the monomers may suitably be diacids (e.g. adipic acid, diglycolic acid), diols (e.g. propylene glycol, butane diol, or unsaturated diols like for instance hydroxyl propyl fumarates), addition monomers (e.g. spiro monomers, isocyanates, divinyl ethers), Anhydrides (e.g. sebacic anhydride).

- 25 The at least one other bioresorbable monomer component of the polymer composition according to the present invention may include a number of different monomers, in equal or different amounts.

Aptly the ratio of glycolic acid to bioresorbable monomer or monomers may be 95%PGA to 5% other monomer(s).

Typically the ratio of glycolic acid to other bioresorbable monomer/monomers will be 70:30%, 75:25%, 80:20%, 90:10%, 95:5% or 98:2%

- 5 Aptly there will be greater than 70% glycolic acid, in the polymer composition according to the present invention but aptly could also be greater than 75, 80, 90 or 95% glycolic acid to other bioresorbable monomer/monomers.

Thus the bioresorbable monomer/monomers percentage may be
10 aptly between 30 to 1%, 25 to 1%, 20 to 1%, 15 to 1%, 10 to 1% or 5 to 1%.

The polymer compositions of the invention are useful for the production of medical devices, particularly implantable devices where it is desirable or necessary that the implant is resorbed by the
15 body. Thus, artefacts in accordance with the present invention include sutures; tissue-engineering scaffolds or scaffolds for implantation; orthopaedic implants; reinforcing agents for long fibre composites used in resorbable load bearing orthopaedic implants; complex shaped devices, for example formed by injection moulding
20 or extruding composites formed by mixing short lengths of chopped fibres with poly-lactic acid; or bone fixation devices, for example formed from relatively large diameter rods (e.g., greater than 1mm) of the compositions of the invention.

The invention will now be illustrated by the following example.

25

Example 1

PGA:PLA co-polymer (98% PGA, 2% PLA) was extruded into a water bath to produce a translucent fibre of approx 0.5mm diameter. This fibre was then suspended vertically and a weight of 200g was

applied. A heated cylinder of brass with a hole of approx
15mm apart from a small section with a 2mm diameter hole, through
which the PGA fibre passes, was heated to a temperature of 90°C
and moved along the fibre at a speed of 200 mm/min. The fibre
5 produced was found to have a strength of greater than 1200 MPa
and a modulus of greater than 20 GPa.

Example 2

A PGA – PLLA (poly-glycolic acid – poly L-lactide) (95:5%) co-
polymer was extruded into a water bath to produce a translucent
10 fibre of approximately 0.48mm diameter. This fibre was then
suspended vertically and a weight of 100g was applied. A heated
cylinder of brass with a hole of approximately 15mm apart from a
small section with a 2mm diameter hole, through which the PGA
fibre passes, was heated to a temperature of 90°C and moved along
15 the fibre at a speed of 500mm/min.

The resultant fibre was tested in tension using an Instron 5566
machine fitted with a 100N load cell. Two pieces of the fibre were
drawn and tested, the results are:

20	Strength/MPa	Modulus/GPa
Fibre 1	1154	21.4
Fibre 2	1115	20.8